

REMARKS

I. Status of the Claims

Claims 71, 72 and 80-83 are pending. Claims 71, 72 and 80-83 are rejected. Claims 71, 80 and 82 have been amended in the amendments presented above.

Applicants respectfully request reconsideration of the claims in view of the following remarks.

II. Each of Claims 80, 81 and 83 Meets the Definiteness Requirement of 35 U.S.C. § 112

Claims 80, 81 and 83 are rejected under § 112, second paragraph.¹ Applicants traverse the rejection in view of the amendments to claim 80.

Claim 80 has been amended above, without any change in scope or content, to clarify the subject matter of this claim. In particular, claim 80 has been amended to recite “detecting a change in capacitance, resistance or acoustic wave of said solid phase support upon contacting of the material with the biosensor device.” Thus, a change in capacitance, resistance or acoustic wave of a solid support of a biosensor device is detected when the material suspected of containing endotoxin is contacted with the biosensor device comprising endotoxin binding protein immobilized on the solid support.

With respect to the “changes in standard solution of endotoxin binding protein,” claim 80 has been amended to recite “correlating the change in the capacitance, resistance or acoustic wave with a change in capacitance, resistance or acoustic wave observed with standard solutions of endotoxin binding protein.” The capacitance, resistance or acoustic wave observed with standard solution of endotoxin binding protein may be used as a reference for comparison with values obtained using the material suspected of containing endotoxin.

Accordingly, claim 80, and dependent claims 81 and 83, meet the definiteness requirement of 35 U.S.C. § 112, second paragraph. Applicants request withdrawal of the rejection.

¹ In the Office Action claims 80-83 were rejected. However, claim 82 depends from claim 71 and not from claim 80. Accordingly, Applicants believe that the rejection only applies to claims 80, 81 and 83.

III. Claims 71-72 and 82 are Patentable over Harris

Claims 71-72 and 82 are rejected under § 102(b) over Harris (US 3,944,391). Applicants respectfully traverse the rejection.

Harris fails to disclose a biosensor device comprising an endotoxin binding protein immobilized on a solid phase support wherein said endotoxin binding protein is from horseshoe crab *Limulus polyphemus* and has the amino acid sequence of SEQ ID NO:1. Instead, Harris discloses endotoxin bound to a synthetic plastic polymer which is itself capable of adsorbing the endotoxin. See col. 3, lines 25-30. A synthetic plastic polymer with bound endotoxin is not the same as a biosensor device comprising endotoxin binding protein immobilized on a solid support.

Accordingly, Harris fails to disclose all the elements of claims 71-72 and 82, which renders Harris incapable of anticipating any of claims 71-72 or 82. Applicants respectfully request withdrawal of the rejection.

IV. Claims 71-72 and 80-83 are Patentable over Levin in view of Rice

Claims 71-72 and 80-83 are rejected under § 103(a) over Levin (US 3,915,805) in view of Rice (US 4,236,893). Applicants respectfully traverse the rejection.

The combination of Levin and Rice fails to teach or suggest all the elements of claims 71-72 and 80-83. Levin is directed to an *in vitro* turbidity assay for detecting endotoxin. Endotoxin is detected by admixing lysate of plasma-free *Limulus* amoebocytes with a sample and measuring an increase in turbidity. See claim 1 of Levin. Nowhere does Levin expressly disclose the use of an endotoxin binding protein immobilized on a solid support. In particular, Levin does not teach or suggest use of a solid support to immobilize any protein.

The deficiencies of Levin are not cured by Rice. Rice discloses measurement of antibodies in a sample using an antigen coated piezoelectric oscillator. See Abstract of Rice. Nowhere does Rice teach or suggest a biosensor device comprising an endotoxin binding protein immobilized on a solid support.

In contrast, claims 71-72 and 80-83 each recite a biosensor device comprising endotoxin binding protein immobilized on a solid support or use of such a device. The failure of the combination of Levin and Rice to teach or suggest all the elements of claims 71-72 and 80-83 indicates no *prima facie* case of obviousness has been established.

In addition, there is no suggestion or motivation to combine these citations. The Examiner asserts that “the association between protein from horseshoe crab and endotoxin is similar to antibody/antigen binding.” Even assuming *arguendo* that this statement is accurate, simply because a physical association process in two or more citations may be similar does not automatically render the citations combinable. Instead, the proper test is whether there is some specific motivation or suggestion in Levin to modify Levin with the method of Rice. Because no such suggestion or motivation has been identified, no *prima facie* case of obviousness has been established.

Also, no reasonable expectation of success has been provided. That is, the Examiner has provided no objective evidence that supports successful modification of the turbidity assay of Levin using the methods taught by Rice. Accordingly, no *prima facie* case of obviousness has been established.

Applicants respectfully request withdrawal of the rejection.

V. Claims 71-72 and 80-83 are Patentable over Levin in view of Oliveira

Claims 71-72 and 80-83 are rejected under § 103(a) over Levin (US 3,915,805) in view of Oliveira (US 4,242,096). Applicants respectfully traverse the rejection.

The combination of Levin and Oliveira fails to teach or suggest all the elements of claims 71-72 and 80-83. As discussed above, the turbidity assay of Levin is insufficient in that it fails to teach or suggest any endotoxin binding protein immobilized on a solid support.

Oliveira fails to cure the deficiencies of Levin. Similar to Rice, Oliveira discloses a piezoelectric oscillator coated with antigen. See Abstract. Nowhere does Rice teach or suggest a biosensor device comprising an endotoxin binding protein immobilized on a solid support.

In contrast, claims 71-72 and 80-83 each recite a biosensor device comprising endotoxin binding protein immobilized on a solid support or use of such a device. The failure of the combination of Levin and Oliveira to teach or suggest all the elements of claims 71-72 and 80-83 indicates no *prima facie* case of obviousness has been established.

In addition, there is no suggestion or motivation to combine Levin and Oliveira. The Examiner asserts that “the association between protein from horseshoe crab and endotoxin is similar to antibody/antigen binding.” Even assuming *arguendo* that this statement is accurate, the presence of a similar physical association process in two or more citations does not automatically render the citations combinable. Instead, the proper test is whether there is some specific motivation or suggestion in Levin to modify Levin with the method of Oliveira. Because no such suggestion or motivation has been identified, no *prima facie* case of obviousness has been established.

Also, no reasonable expectation of success has been provided. That is, the Examiner has provided no objective evidence that supports successful modification of the turbidity assay of Levin using the methods taught by Oliveira. Accordingly, no *prima facie* case of obviousness has been established.

Applicants respectfully request withdrawal of the rejection.

VI. Claims 71-72 and 82 are Patentably Distinct from claims 1-3 of US 6,222,021

Claims 71-72 and 82 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. 6,222,021.² Applicants respectfully traverse the rejection.

Claims 1-3 of U.S. 6,222,021 are directed to a fragment of endotoxin binding protein of SEQ ID NO: 3. In contrast, claims 71, 72 and 82 are directed to a biosensor device comprising an endotoxin binding protein immobilized on a solid phase support wherein said endotoxin

² Applicants note that the rejection was for claims 71-72. However, claim 82 depends from claim 71, and Applicants believe that claim 82 should have been included in this rejection and not in the double patenting rejection discussed below in Section VII.

binding protein is from a horseshoe crab *Limulus polyphemus* and has the amino acid sequence of SEQ ID NO:1.

Claims 71-72 and 82 are distinct from claims 1-3 of U.S. 6,222,021. For example, the specification states in the "Brief Description of Figures" that endotoxin binding protein isolated from *Limulus polyphemus* refers to SEQ ID NO:1 (see FIG. 15 description). The specification also states in the "Brief Description of Figures" that SEQ ID NO:3 refers to a modified endotoxin binding/neutralizing protein having the tetrapeptide Glu-Ala-Glu-Ala attached to its N-terminus. Thus, SEQ ID NO:1 and SEQ ID NO:3 are different proteins. Accordingly, claims 1-3 of U.S. 6,222,021 and instant claims 71, 72 and 82 are patentably distinct because they are directed to different proteins.

Applicants respectfully request withdrawal of the rejection.

VII. The Double Patenting Rejection of Claims 80, 81 and 83 is Improper

Claims 80, 81 and 83 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 of U.S. 6,222,021 in view of Oliveira (US 4,242,096) and Levin (US 3,915,805).³ Applicants respectfully traverse the rejection.

The subject matter of independent claim 80 was originally present at the time of filing of at least one of the priority applications. See, for example, claim 80 as presented in U.S. 07/883,457 filed on May 15, 1992. U.S. 07/883,457 was subject to a restriction requirement (see Paper No. 9 in U.S. 07/883,457) and the Group including claim 80 (Group V) was not elected in response to the restriction requirement. Independent claim 80 has been presented in the instant application to pursue non-elected subject matter.

M.P.E.P. 804.01 and 35 U.S.C. § 121 are clear in stating that a double patenting rejection is prohibited where a restriction requirement has been issued. Accordingly, the double patenting rejection of claims 80, 81 and 83 is improper and should be withdrawn.


³ Applicants believe this rejection to be improper, as a double patenting rejection requires common ownership of the cited patent(s) and the pending patent application. See M.P.E.P. 804. The assignee of the instant application does

VIII. Conclusion

In view of the foregoing amendments and remarks, all claims in the application are in condition for allowance, and mailing of a Notice of Allowance is respectfully requested.

Respectfully submitted,
For Wainwright et al.

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not currently own, or never has owned, Oliveira (US 4,242,096) or Levin (US 3,915,805). Accordingly, Applicants remarks above are in response to U.S 6,222,021.